Chlorination, Chlorination By-products, and Cancer: A Meta-analysis

ABSTRACT

Objectives. Individual epidemiological investigations into the association between chlorination by-products in drinking water and cancer have been suggestive but inconclusive. Enough studies exist to provide the basis for a meaningful meta-analysis.

Methods. An extensive literature search was performed to identify pertinent case-control studies and cohort studies. Consumption of chlorinated water, surface water, or water with high levels of chloroform was used as a surrogate for exposure to chlorination by-products. Relative risk estimates were abstracted from the individual studies and pooled.

Results. A simple meta-analysis of all cancer sites yielded a relative risk estimate for exposure to chlorination by-products of 1.15 (95% CI: 1.09, 1.20). Pooled relative risk estimates for organ-specific neoplasms were 1.21 (95% CI: 1.09, 1.34) for bladder cancer and 1.38 (95% CI: 1.01, 1.87) for rectal cancer. When studies that adjusted for potential confounders were pooled separately, estimates of relative risks did not change substantially.

Conclusions. The results of this meta-analysis suggest a positive association between consumption of chlorination by-products in drinking water and bladder and rectal cancer in humans. (*Am J Public Health.* 1992;82:955–963)

Robert D. Morris, MD, PhD, Anne-Marie Audet, MD, MS, Italo F. Angelillo, DDS, MPH, Thomas C. Chalmers, MD, and Frederick Mosteller, PhD

Introduction

After its first use in the Chicago stockyards in 1908, chlorination of drinking water spread rapidly throughout the United States and produced dramatic reductions in morbidity and mortality associated with waterborne disease.[1] Since then, chlorine has remained the method of choice for water purification; it is currently added to approximately 75% of the nation's drinking water.[2] In 1974, Rook[3] discovered that the combination of chlorine with organic compounds in drinking water produced halogenated organic compounds—chloroform, in particular. In 1975, the National Organics Reconnaissance Survey[4] verified that chlorination by-products were a major contaminant of chlorinated surface water. The study also showed that chloroform concentration correlates highly with the concentrations of other halogenated hydrocarbons and is, therefore, a useful indicator for the presence of these compounds. Since this finding, a plethora of epidemiological studies[5–27] have investigated possible associations between consumption of chlorinated water and cancer. These studies consider a wide range of populations and regions and demonstrate somewhat inconsistent patterns of association. We used meta-analytic methods to pool the results of these studies in an attempt to further our understanding of the relationship between water chlorination and neoplastic diseases. Meta-analysis provides greater statistical power and greater resolution in the estimation of relative risks than do individual studies.

Methods

Identification of Relevant Studies

To identify references pertaining to the relationship between chlorination of drinking water and neoplastic diseases, we used the Medline data retrieval system to search the medical, public health, and biological literature from 1966 through 1991. Relevant papers were obtained and reviewed to locate additional references. Because initial analyses suggested an association between chlorination and both bladder and rectal cancer, the Medline system was used to conduct a second search of the literature over the same 25-year period for papers that considered these neoplasms and mentioned water in the title, abstract, or keywords.

Only those studies that identified morbidity or mortality as well as exposure and potential confounders at the level of the individual (i.e., case-control or cohort studies) were included in the meta-analysis. Studies that considered incidence and exposure at the level of a region or community (i.e., ecological studies) were excluded.

Quality Scoring and Exposure Assessment

Each article was blinded as to authors, institutions, journal, and study re-

Robert D. Morris is with the Division of Biostatistics, Medical College of Wisconsin, Milwaukee, Wis. Anne-Marie Audet is with the American College of Physicians, Philadelphia, Pa. Italo F. Angelillo is with the Institute of Hygiene and Preventive Medicine at the Universita Degli Studi di Napoli Fredrico II, Naples, Italy. Thomas Chalmers and Frederick Mosteller are with the Technology Assessment Group, Harvard University School of Public Health, Boston, Mass.

Requests for reprints should be sent to Robert D. Morris, MD, PhD, Division of Biostatistics, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226.

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sults. Two independent readers scored each paper for quality, using a scoring system that incorporates elements of systems developed by Chalmers et al.[28] and Longnecker et al.[29] Studies were scored on the basis of selection of subjects, measurement of and adjustment for confounding variables, exposure assessment, and statistical analysis. The overall quality score was calculated from three subscores: a general methods score, a data analysis score, and an exposure assessment score. Each subscore was calculated as the percentage of applicable quality criteria that were met in each study. The criteria employed are listed with the results. The cumulative quality score was a weighted average of the three scores, with both general methods and exposure assessment receiving twice the weight of the data analysis score.

Exposure assessment is the most difficult task in a study of this kind. Three factors determine a person's cumulative exposure to an environmental contaminant or risk factor: (1) the environment to which the person was exposed, (2) the level of the proposed agent present in the environment, and (3) the degree to which the person is exposed to that environment. In the current context, these exposures refer to (1) the source of tap water, (2) concentrations of chlorination by-products in that tap water, and (3) the amount of tap water consumed. Although exposure at a fixed point in time (e.g., the time of diagnosis or death) often correlates highly with lifetime exposure, a complete assessment of exposure must also include the historical records for each of these three factors. Thus there are six factors that must be evaluated in each study: three exposure factors plus historical records for each of these factors. The quality of exposure assessment was scored for each study as the percentage of these factors that were evaluated in the study.

Most of the identified studies used consumption of surface water as an indirect measure of exposure to chlorination by-products. Unchlorinated natural waters do not contain significant amounts of chlorinated hydrocarbons. Consequently, the comparison of consumers of chlorinated water with consumers of unchlorinated water provided an acceptable surrogate for comparing exposure vs nonexposure to chlorination by-products.

Similarly, chlorinated surface water contains more chlorination by-products than does groundwater. Whereas virtually all surface water is chlorinated, groundwater tends to be less heavily chlorinated, and in the case of private wells the water is often unchlorinated. In addition, groundwater contains less organic matter than does surface water. Organic matter combines with chlorine to form chlorination by-products. Measurements of chlorination by-products in the drinking water supply[2] have shown that chlorinated surface water contains much higher levels of these by-products than does chlorinated groundwater (medians of 50.7 and 0.8 ppb, respectively) even when the surface water is drawn from protected reservoirs. For these reasons, consumption of surface water vs groundwater was also used as a surrogate for exposure to chlorination by-products.

Although most of the studies used either consumers of groundwater or consumers of unchlorinated water for the control group, one study[22] used consumers of chloraminated water as the control group. Chloramination is a process whereby both chlorine and ammonia are added to filtered drinking water to form chloramines. This chloramine residual is intended to provide sufficient bactericidal capacity to maintain water purity in the distribution system without introducing large amounts of free chlorine. This is a process that minimizes the formation of chlorination by-products. Therefore, this comparison of chlorinated with chloraminated water consumption provided a surrogate for exposure vs nonexposure to chlorination by-products.

Chloroform is the most common chlorination by-product and consequently has been the focus of health concerns related to water chlorination. Several studies included measured chloroform levels in their exposure assessments. Although recent research[30] suggests that other by-products may be more toxic, chloroform concentration correlates well with the concentration of other by-products.[4] Therefore, measures of chloroform concentrations were deemed to be the most accurate measures of chlorination by-products.

Extraction of Relative Risk Estimates

The odds ratios or relative risks for cancer among consumers of drinking water containing chlorination by-products were identified for each of the selected studies. Exposure was defined on the basis of the categorization of subjects as consumers of chlorinated water or surface water in the individual studies; nonexposure was defined on the basis of the categorization of subjects as consumers of nonchlorinated water, chloraminated water, or groundwater. When risks were stratified by sex, they were recorded as such. The variance of the natural log of the odds ratio or relative risk was derived with the statistics provided in the particular study. If an odds ratio was reported to be different from unity with P less than a specified significance level, the variance was calculated assuming P equal to this maximum value (e.g., given $P < .05$, $P = .05$ was assumed). Calculation of a variance on the basis of this conservative assumption resulted in the maximum possible variance and minimized the probability of a type I error in the meta-analyses. If a study reported a coefficient from a logistic regression, the regression coefficient was used along with an estimate of average exposure for the exposed sample to calculate an estimate for the relative risk. Studies that stratified according to level of exposure were analyzed by pooling the values from each stratum to yield a single value from each study estimating the relative risk for the exposed vs nonexposed populations.

The neoplasms considered in these studies were sufficiently rare that odds ratios were deemed to be close approximations of relative risks. Therefore, we did not distinguish between odds ratios and relative risks in our meta-analysis. All results listed may be considered as relative risk estimates.

Some studies reported morbidity data and others reported mortality data. For relative risks for mortality to differ from relative risks for morbidity, the exposure in question must alter disease survival. We have no reason to expect that water chlorination alters disease survival. To evaluate this possible bias, we analyzed the two groups separately as part of the sensitivity analysis described below.

Meta-analysis

The relative risk estimates were analyzed in two stages, a meta-analysis of all studies and a meta-analysis of selected subgroups of studies. In the first stage, meta-analyses were performed for each cancer site by pooling all pertinent studies without stratifying for sex. If a given tumor site was evaluated in at least two studies, relative risk estimates were pooled and analyzed for that site. The random effects model described by DerSimonian and Laird[31] was used to combine the collected values. This procedure yielded a single estimate of the relative risk for or-

gan-specific neoplasms in individuals exposed to chlorination by-products in drinking water.

Meta-analysis, in addition to improving our ability to identify small but significant relative risks in the context of apparently contradictory research findings, enhances our capacity to interpret truly negative results. Statistical power is a measure of the probability of finding a significant difference, assuming a specified effect and a specified type I error rate. A detailed analysis of statistical power was carried out for each cancer site. For each negative result ($P > .05$) the probability of detection of relative risks of 1.2, 1.4, and 1.6 was determined on the basis of the calculated relative risk estimate and variance.

Sensitivity and Dose-Response Analyses

If the first analysis demonstrated a significant association ($P < .05$) between chloroform exposure and neoplastic disease for a given site, a second set of more detailed analyses was performed on relative risk estimates pertaining to that site. The influence of potential confounding variables, sex differences, quality score, and accuracy of exposure assessment on the effect of chlorination by-products were all evaluated in this stage. In addition, studies that provided dose-response relationships were pooled separately.

The effect of inaccurate determination of exposure to chlorination by-products (misclassification bias) and the effect of incomplete control for confounding variables were of particular concern. The authors of each study chose to adjust for a slightly different set of potential confounding variables. A failure to adjust for some factor (e.g., smoking in bladder cancer) might well lead to erroneous estimates of risk. To determine whether such differences among studies might have an impact on the pooled results, individual studies that controlled for confounders were grouped for separate meta-analyses. The relative risk estimates of cancer for each site were also pooled separately for each sex. Studies were also divided into two groups and analyzed according to their score for overall quality and for quality of exposure assessment. In each case, studies with scores above the mean were compared with studies whose scores were below the mean.

A conventional literature review pools findings implicitly by weighting according to a subjective and unspecified quality scoring system. Although weighting by quality score is intuitively appealing, there is no established protocol either for calculating a quality score or for weighting according to score. As a simple test, we repeated the meta-analyses for bladder and rectal cancer, using quality scores as weights.

Meta-analysis was also used to evaluate dose-response relationships. For each study that stratified by level of exposure, relative risk estimates for high, medium, and low levels of exposure were determined. The studies were then combined, with each level pooled separately.

The dose-response analysis excluded those studies that evaluated exposure as a dichotomous variable. In order to determine the impact of this exclusion, we repeated the dose-response analysis with these studies included. In order to include these studies, we assumed that the exposed group in studies with dichotomous exposure measures had experienced moderate levels of exposure.

Results

Literature Search

The literature search identified 10 case-control studies[15–24] and two cohort studies[25,26] that investigated the relationship between some measure of exposure to chlorination by-products in the drinking water and cancer. One case-control study[19] considered source of drinking water as one of many potential risk factors for bladder cancer. The association between bladder cancer and drinking water was stated to be nonsignificant, but numerical results were not reported, making the inclusion of this study in the meta-analysis impossible. One cohort study considered bladder cancer in a group of workers with exposure to a known carcinogen. This cohort was deemed not to represent the general population and was also excluded. The 10 studies that were entered into the meta-analysis are listed in Table 1.

One study[22] evaluated a variety of neoplasms and found an association between bladder cancer and chlorination. It was followed by a second study[27] that analyzed the same sample with more thorough methods for assessment of exposure to chlorination by-products. The second study reported two odds ratios, one comparing high exposure to no exposure and the other comparing moderately high to moderately low exposure. The second of these two odds ratios was used in the analyses of bladder cancer except in the dose-response analysis, in which both values were used.

Quality Scoring

Table 2 shows the results of the quality scoring procedure. All 10 studies identified the source of drinking water at the residences of the subjects either at the time of the study or at the time of death. Chloroform concentrations and specific tap water consumption rates for the subjects were determined in a minority of the studies (4 in both cases). Historical patterns of drinking water consumption were not quantified in any of the studies. Historical sources of tap water were evaluated in 6 of the studies. No study used historical values of chlorination by-product concentrations, because these are not generally available, but 7 used some portion of the historical record, such as water utility chlorination logs, to estimate historical levels of chlorination by-products in drinking water. The studies are listed in Table 1 in order of their quality scores.

Selection of cases and controls followed accepted procedures and was not a major source of bias in these studies. Information bias associated with failure to adjust for confounding variables may have been more of a problem. With the exception of age (100%), sex (100%), population density (80%), and race (60%), potentially confounding variables were not generally adjusted for. Statistical analyses in these studies were usually thorough with regard to the determination of relative risks, but they tended to be less rigorous with regard to analyzing other aspects of the sample groups. Although most studies listed *P* values (70%), adjusted for confounders (90%), and identified specific tests used (80%), few listed or analyzed demographic data (40%). Only one study (10%) provided power calculations.

Extraction of Risk Estimates and Meta-analysis

Table 3 lists the relative risk estimates extracted from each study. Although 39 of these 64 estimates (64%) are greater than 1.00, only 19 (30%) are significantly greater than 1.00 ($P < .05$).

Table 4 lists the results of the organ-specific meta-analyses, with power calculations. Bladder cancer has an overall relative risk estimate of 1.21 (95% CI: 1.09, 1.34). Rectal cancer has a relative risk estimate of 1.38 (95% CI: 1.01, 1.87). Lung, breast, brain, kidney, liver, pancreatic, esophageal, colonic, and gastric neoplasms all have pooled estimates of relative risk that are not significantly different from unity.

Note that all 12 relative risk estimates were greater than 1.00, suggesting that the

TABLE 1—Summary of Studies Included in the Meta-analysis Relating Chlorination By-products in Drinking Water to Cancer

Authors	Year[a]	Population	Cases	Controls	Exposure Assessment	Covariates	Analysis
Cantor et al.[23]	1987 (78)	White residents of 10 US regions	2982 newly diagnosed, cases of bladder cancer	Community controls matched 2:1 for age, sex, and region by random dialing and Medicare files	History of residence, and beverage consumption combined with survey and sampling of water utilities	Age, sex, cigarette consumption, occupation, population of place of longest residence	Logistic regression
Young, Wolf, Kanarek[24]	1987 (75)	Wisconsin residents	347 newly diagnosed cases of colon cancer	General population controls matched 2:1 for age and sex	Water consumption by interview and chloroform by historical records and measurement	Age, sex, population of place of residence	Logistic regression
Zierler, Danley, Feingold[22,27 b]	1986, 1988 (22, 71)	Massachusetts residents	51 645 kidney, bladder, stomach, pancreas, colon, lung, breast cancer deaths	Deaths from cardiovascular, cerebrovascular, or pulmonary disease or lymphatic cancer by death certificate	Chlorination/ chloramination at address on death certificate	Age, sex, surface/ groundwater, population density, and level of poverty in county of residence	Odds ratios with Mantel-Haenszel adjustment
Cragle, Shy, Struba, Siff[21]	1985 (65)	Patients of 7 North Carolina hospitals	200 newly diagnosed cases of colon cancer	Noncancer hospital controls matched 2:1 for age, sex, vital status, and hospital	Years of exposure to chlorinated water by residential history and survey of water utilities	Age, sex, genetic risk, dietary fiber, region, urban residency, smoking, alcohol use, education, number of pregnancies	Logistic regression
Lawrence, Taylor, Trock, Reilly[20]	1984 (62)	New York female teachers	395 colorectal cancer deaths	Noncancer deaths matched 1:1 for age and sex by death certificate	20-year employment and residential history with model for chloroform levels	Age, marital status, population density, type of surface water	Logistic regression
Wilkins, Comstock[25 c]	1981 (61)	31 000 residents of Washington County, MD	Diagnosis of cancer in 12 years following initial survey	*Unexposed:* Deep well users	*Exposed:* Users of chlorinated surface water in Hagerstown, Md	Age, sex, smoking, marital status, education	Logistic regression
Gottlieb, Carr, Clarkson[18]	1982 (49)	Louisiana residents	10 205 kidney, bladder, stomach, liver, and colorectal cancer deaths	Two groups of cancer deaths and one of noncancer deaths matched 1:1 for age, sex, race, and parish by death certificate	Chlorinated/ unchlorinated water at address on death certificate and at birthplace	Groundwater/surface water, cardiovascular disease	Stratified odds ratio with χ^2 test
Brenniman, Lagos, Amsel, Namekata, Wolff[16]	1980 (46)	White residents of Illinois	3208 gastro-intestinal and urinary tract cancer deaths	Noncancer deaths matched 14:1 for age, sex, and county by death certificate	Chlorinated/ unchlorinated water at address on death certificate	Urbanicity, population density	Odds ratios with Mantel Haenszel adjustment
Young, Kanarek, Tsiatis[17]	1981 (45)	White female residents of Wisconsin	8029 cancer deaths	Noncancer deaths matched 1:1 for age, sex, race, and county by death certificate	Chlorinated/ unchlorinated water at address on death certificate	Population density, occupational risk, marital status, rural runoff in water	Logistic regression
Alvanja, Goldstein, Susser[15]	1978 (43)	NY State residents	3446 gastro-intestinal and urinary tract cancer deaths	Noncancer and lung cancer deaths matched 1:1 for age, sex and county by death certificate	Chlorinated/ unchlorinated water at address on death certificate	Urbanicity, occupation	Stratified odds ratio with χ^2 test

Note. Studies are listed in descending order with respect to the quality score. (Scores are presented in parentheses after the year.)
[a]Overall quality scores that are listed with the year may range from 0 to 100.
[b]The second Zierler study[27] was conducted on the same population, but was limited to bladder cancer. Note that this study had a substantially higher quality score than the earlier study (71 vs 22).
[c]Wilkins and Comstock's study was a cohort study. All other studies listed were case-control studies.

association of chlorination by-products with cancer, although modest, is more general than the two statistically significant sites. Pooling all 12 sites yields an estimate of the overall relative risk for cancer associated with chlorination by-products in drinking water of 1.15 ($P < .0001$). Eliminating bladder, rectal, and colorectal cancer and repeating this overall meta-analysis results in a relative risk estimate of 1.09 ($P = .006$).

The power of the negative meta-analyses to detect a relative risk of 1.2 at a significance level of .05 ranges from .27 for breast cancer to .70 for pancreatic cancer, compared with a power of only .06 for brain tumors. For a relative risk greater than 1.6, power for all of the sites with negative findings rises above .90, with the exception of that for brain cancer, which only reaches .18.

Sensitivity and Dose-Response Analyses

Of the sites listed, only bladder and rectal cancer met the established criteria for further analysis. In addition, colonic neoplasms were included in these analyses to evaluate the apparent differences between risks for colonic and rectal neoplasms given the anatomic and physiologic relationship between the two sites. For bladder cancer, the effects of adjusting for smoking, occupation, or population density were evaluated. For rectal and colon cancer, only population density was analyzed (other risk factors, such as diet, were not included in the studies selected). Table 5 lists the results of these analyses.

For bladder cancer, adjustments for confounders do not appear to alter the association with exposure to chlorination by-products. Separate meta-analyses of studies that adjusted for population density, smoking, or occupation yielded relative risk estimates of 1.20, 1.25, and 1.22, respectively. The single study that adjusted for all three factors had a relative risk estimate of 1.19. Estimates of relative risk for bladder cancer were 1.17 for females and 1.24 for males.

The bladder cancer studies with quality scores above the average for this group had a pooled relative risk estimate of 1.25 (95% CI: 1.08, 1.45). Those with below-average quality scores had a pooled value of 1.16 (95% CI: 0.96, 1.40). Improved exposure assessment increases the estimate of relative risk and narrows the confidence limits around this estimate from 1.16 (95% CI: 0.96, 1.40) to 1.25 (95% CI 1.09, 1.45).

TABLE 2—Items Used in Quality Scoring for Case-Control and Cohort Studies of the Association between Consumption of Chlorination By-products in Drinking Water and Cancer

Quality Scoring Item	Studies Complying, %[a]
Case and control selection	
Random selection of cases	90
Selection blinded to exposure status	70
Specific disease criteria given	100
Disease validated by histology or other "gold standard"	40
No known association between control status and exposure	70
Random selection of controls	80
Adjustment or matching for confounders	
Age	100
Sex	100
Population density	90
Race	60
Smoking	40
Occupation	40
Diet	10
Exposure assessment	
Drinking water source for study subjects identified	100
Tap water consumption for study subjects assessed	40
Chloroform in drinking water sources measured	40
Historical drinking water sources for subjects evaluated	60
Historical patterns in tap water consumption for subjects evaluated	0
Historical chlorination levels in water sources evaluated	70
Data analysis	
Power calculation performed	10
Demographic data listed	40
Statistical analysis of demographic data	10
Correlations between independent variables listed	20
Precise *P* values listed	70
Test specified	80

[a]If compliance is not specifically indicated in the text, noncompliance is assumed.

For rectal cancer, adjustments for confounders do not appear to alter the association with exposure to chlorination by-products. Separate meta-analysis of studies that adjusted for population density yielded a relative risk estimate of 1.33. Estimates of relative risk for rectal cancer were 1.11 for females and 1.24 for males.

The rectal cancer studies with quality scores above the average for this group had a pooled relative risk estimate of 1.91 (95% CI: 1.56, 2.35). Those with below-average quality scores had a pooled value of 1.07 (95% CI: 0.89, 1.29). Improved exposure assessment increases the estimate of relative risk from 1.23 (95% CI: 0.89, 1.70) to 1.57 (95% CI: 1.09, 2.24).

A different picture emerges with regard to colon cancer. No grouping of studies, either by sex or by adjustment for population density, results in a significant estimate of relative risk for colon cancer. In the quality score breakdown, high-quality-score studies had lower risk estimates than did low-quality-score studies (1.10 [95% CI: 0.79, 1.53] vs 1.13 [95% CI: 0.86, 1.48]).

Weighting by quality score alone produced relative risks of 1.34 for bladder cancer and 1.46 for rectal cancer (95% CIs: [1.20, 1.49] and [1.29, 1.64], respectively).

Estimates of relative risk for bladder, colon, and rectal cancer at low, medium, and high exposure levels are shown in Table 6. The values for bladder cancer rise steadily from 1.03 to 1.20 to 1.41 and demonstrate increasing levels of significance with increasing exposure level. Rectal cancer also shows a pattern of increasing relative risk with increasing cumulative exposure from 1.13 to 1.29 to 2.04. The inclusion of studies with dichotomous measures of exposure produces estimates of relative risk for moderate exposure that fall, in each case, between the estimates for high and low exposure.

A comparison between studies evaluating incidence and those evaluating mortality did not show a substantial difference between the two categories. For bladder cancer, the pooled relative risk estimates were 1.22 (95% CI: 1.03, 1.44) for the five mortality studies and 1.24 (95% CI: 0.92, 1.67) for the two incidence stud-

TABLE 3—Estimates of the Relative Risk for Neoplasia Associated with the Consumption of Chlorination By-products in Drinking Water as Extracted from Individual Studies and Grouped by Cancer Site

Author	Year	Site	Sex	Relative Risk Estimate	95% CI
Alvanja	1978	Bladder	MF	1.69	1.07, 2.67
Brenniman	1980	Bladder	MF	0.98	0.77, 1.25
Young	1981	Bladder	F	1.15	0.70, 1.89
Gottlieb	1982	Bladder	MF	1.18	0.95, 1.45
Wilkins	1986	Bladder	MF	2.20	0.71, 6.82
Cantor	1987	Bladder	MF	1.19	1.07, 1.32
Zierler	1988	Bladder	MF	1.40	1.20, 2.10
Young	1981	Brain	F	2.13	1.13, 4.04
Gottlieb	1982	Brain	MF	0.85	0.67, 1.09
Young	1981	Breast	F	1.25	0.99, 1.58
Gottlieb	1982	Breast	F	1.19	1.01, 1.42
Zierler	1986	Breast	F	0.89	0.85, 0.93
Wilkins	1986	Breast	F	2.27	1.16, 4.44
Alvanja	1978	Colon	MF	1.61	1.15, 2.24
Brenniman	1980	Colon	MF	1.11	0.99, 1.25
Young	1981	Colon	F	1.52	1.25, 1.85
Gottlieb	1982	Colon	MF	1.01	0.84, 1.20
Cragle	1985	Colon	MF	0.10	0.01, 0.79
Zierler	1986	Colon	MF	0.89	0.86, 0.92
Wilkins	1986	Colon	MF	0.89	0.57, 1.39
Alvanja	1978	Colorectal	MF	1.71	1.31, 2.24
Brenniman	1980	Colorectal	MF	1.13	1.02, 1.26
Young	1981	Colorectal	F	1.45	1.22, 1.73
Gottlieb	1982	Colorectal	MF	1.40	0.73, 2.69
Lawrence	1984	Colorectal	F	0.97	0.74, 1.27
Zierler	1986	Colorectal	MF	0.92	0.85, 0.99
Wilkins	1986	Colorectal	MF	1.03	0.67, 1.58
Young	1987	Colorectal	MF	0.90	0.60, 1.35
Alvanja	1978	Esophagus	MF	2.12	1.10, 4.08
Brenniman	1980	Esophagus	MF	0.97	0.68, 1.38
Young	1981	Esophagus	F	0.95	0.33, 2.76
Gottlieb	1982	Esophagus	MF	1.08	0.78, 1.48
Wilkins	1986	Esophagus	MF	1.76	0.53, 5.84
Young	1981	Kidney	F	0.99	0.69, 1.41
Gottlieb	1982	Kidney	MF	1.49	1.12, 1.99
Zierler	1986	Kidney	MF	1.00	0.90, 1.11
Wilkins	1986	Kidney	MF	2.76	0.67, 11.37
Brenniman	1980	Liver	MF	1.00	0.58, 1.72
Young	1981	Liver	F	1.05	0.75, 1.46
Gottlieb	1982	Liver	MF	1.20	0.93, 1.54
Wilkins	1986	Liver	MF	2.98	0.92, 9.65
Alvanja	1978	Lung	MF	1.79	1.08, 2.97
Young	1981	Lung	F	0.80	0.61, 1.04
Gottlieb	1982	Lung	MF	1.12	0.93, 1.34
Zierler	1986	Lung	MF	0.94	0.91, 0.97
Wilkins	1986	Lung	MF	0.96	0.61, 1.51
Alvanja	1978	Pancreas	MF	1.97	1.23, 3.16
Brenniman	1980	Pancreas	MF	1.02	0.85, 1.23
Young	1981	Pancreas	F	1.15	0.81, 1.64
Gottlieb	1982	Pancreas	MF	1.07	0.88, 1.30
Zierler	1986	Pancreas	MF	0.94	0.89, 0.99
Wilkins	1986	Pancreas	MF	0.80	0.44, 1.45
Alvanja	1978	Rectum	MF	1.93	1.22, 3.05
Brenniman	1980	Rectum	MF	1.22	0.95, 1.56
Young	1981	Rectum	MF	1.21	0.82, 1.78
Gottlieb	1982	Rectum	MF	1.96	1.54, 2.50
Zierler	1986	Rectum	MF	0.96	0.89, 1.04
Wilkins	1986	Rectum	MF	1.42	0.70, 2.88

TABLE 4—Relative Risk Estimates and Power Calculations from the Site-Specific Meta-analyses of the Associations between Exposure to Chlorination By-products and Cancer

Site	n[a]	Relative Risk Estimate	95% CI	P	Power[b] for Detection of Specified Relative Risks ($\alpha = .05$) 1.20	1.40	1.60
Bladder	7	1.21	1.09, 1.34	<.0001	...	...	...
Brain	2	1.29	0.53, 3.14	.56	.06	.11	.18
Breast	4	1.18	0.90, 1.54	.24	.27	.69	.93
Colon	7	1.11	0.91, 1.35	.32	.48	.63	>.99
Colorectal	8	1.15	0.97, 1.37	.10	.54	.97	>.99
Esophagus	5	1.11	0.85, 1.45	.43	.27	.69	.93
Kidney	4	1.16	0.89, 1.51	.23	.27	.71	.94
Liver	4	1.15	0.94, 1.40	.16	.44	.92	>.99
Lung	5	1.01	0.86, 1.18	.94	.27	.69	.93
Pancreas	6	1.05	0.91, 1.22	.48	.70	>.99	>.99
Rectum	6	1.38	1.01, 1.87	.04	...	...	...
Stomach	6	1.14	0.94, 1.38	.19	.46	.93	>.99

[a]Number of studies evaluating specific cancer site.
[b]Power is defined as $1 - \beta$, where β is the probability of type II error at the given levels of true relative risk and significance. Statistical power was not calculated if the meta-analysis was significant.

ies. For rectal cancer, these estimates were 1.37 (95% CI: 0.98, 1.92) for the five mortality studies and 1.42 (95% CI: 0.70, 2.88) for the lone incidence study. This stratified analysis suggests that incidence studies in our analysis do not yield different relative risk estimates from mortality studies.

Discussion

The data support a significant association between bladder cancer and exposure to chlorination by-products in drinking water. This association appears to follow a dose-response relationship. Controlling for potential confounders (i.e., sex, smoking, urban living, and occupational risk) does not diminish this association. The association of rectal cancer with chlorination by-products follows a pattern similar to that of bladder cancer.

The association of chlorination by-products with bladder and colon cancer increases with improved exposure assessment and higher overall study quality. This pattern strengthens the evidence for an association between both rectal and bladder cancer and chlorination by-products and suggests that the true relative risks may be higher than those listed here.

Chlorination by-products are associated with cancer of the rectum, but not cancer of the colon. The bladder and the rectum both serve a similar physiological function by storing concentrated excretory products. One might speculate that the epithelial tissue at both sites is exposed to higher levels of chlorination by-prod-

TABLE 5—Relative Risk Estimates for the Association of Exposure to Chlorination By-products with Cancer of the Bladder and Colon, from Studies Grouped by Sex, Adjustment for Confounders, and Quality Scores

Site	Category	Group	Relative Risk Estimate	95% CI
Bladder	All relevant studies		1.21	1.09, 1.34
	Sex	Females	1.17	1.03, 1.34
		Males	1.24	0.97, 1.57
		Combined[a]	1.22	1.08, 1.37
	Confounders	Population density	1.20	1.08, 1.33
		Smoking	1.25	1.09, 1.45
		Occupation	1.22	1.06, 1.41
	Overall quality score	High	1.25	1.09, 1.45
		Low	1.16	0.96, 1.40
	Exposure quality score	High	1.25	1.09, 1.45
		Low	1.16	0.96, 1.40
Rectum	All relevant studies		1.38	1.01, 1.87
	Sex	Females	1.10	0.90, 1.36
		Males	1.24	0.86, 1.79
		Combined[a]	1.42	0.99, 2.03
	Confounders	Population density	1.33	1.02, 1.73
	Overall quality score	High	1.91	1.56, 2.35
		Low	1.07	0.89, 1.29
	Exposure quality score	High	1.57	1.10, 2.25
		Low	1.23	0.89, 1.70
Colon	All relevant studies		1.11	0.91, 1.37
	Sex	Females	1.19	0.93, 1.53
		Males	1.09	0.81, 1.48
		Combined[a]	1.02	0.86, 1.22
	Confounders	Population density	1.09	0.89, 1.32
	Overall quality score	High	1.10	0.79, 1.53
		Low	1.13	0.86, 1.48
	Exposure quality score	High	1.05	0.72, 1.54
		Low	1.11	0.87, 1.41

[a]This group includes only those studies that considered both sexes. Hence the results are different from the values for all relevant studies.

TABLE 6—Meta-analytic Estimates of the Association between Bladder and Colon Cancer at Specified Levels of Cumulative Exposure to Chlorination By-products

Site	Level of Exposure	Relative Risk Estimate	95% CI
Bladder	Low	1.03	0.85, 1.24
	Moderate[a]	1.20	1.05, 1.37
	Moderate[b]	1.20	1.04, 1.38
	High	1.41	1.24, 1.62
Rectum	Low	1.13	0.61, 2.09
	Moderate[a]	1.29	1.00, 1.67
	Moderate[b]	1.49	1.10, 2.01
	High	2.04	1.18, 3.53

[a]This category includes only data from those studies that ranked a middle level of exposure.
[b]This category includes all studies for which exposure was dichotomous, in addition to studies ranked a middle level of exposure.

ucts and is therefore at increased risk for the development of neoplasia.

The most important potential confounder not adjusted for in these studies is diet. If consumption of a diet high in fat and low in fiber were associated with consumption of chlorinated water, one could argue that the observed association is simply a surrogate for dietary risk. We know of no such association. In addition, if diet were responsible for the observed association with rectal cancer, we would expect to see the same association with colon cancer. The marked differences in these associations tend to refute the contention that diet is an explanatory factor for observed associations.

With regard to other sites for neoplastic disease, relative risks ≤ 1.2 cannot be excluded with a high degree of confidence for any of the sites considered. A relative risk ≥ 1.6 for cancer associated with chlorination by-products can, however, be excluded with a high degree of confidence, on the basis of current evidence, for most sites. The meta-analysis for brain cancer lacks the power to exclude with any certainty even a high relative risk for cancer.

The present study has identified a clear and significant association between neoplastic disease and the consumption of water containing chlorination by-products. Precise cause and effect cannot be determined. The possibility that chlorination may serve as a marker for some other aspect of drinking water quality or an associated geographic or demographic variable cannot be entirely discounted, given the available research. If chlorination by-products are carcinogens, the identity of the compound or compounds involved is unclear. One agent actively being investigated in this context is a chlorinated hydroxy-furanone recently identified as an extremely potent mutagen present in chlorinated surface water.[30]

If we posit that the association demonstrated between chlorination by-products and cancer represents a causal relationship in some way, the positive relative risks identified for bladder and colon cancer can best be interpreted in the context of attributable proportions (i.e., that portion of cases that can be attributed to a given risk factor[32]). By a conservative estimate, based on the 54% of the population that consumes chlorinated surface water (rather than the 75% that consumes chlorinated water), a 21% increase in the risk for bladder cancer and a 38% increase in the risk for rectal cancer translate into attributable proportions of 9% and 15%, respectively. With US incidence rates for bladder and rectal neoplasms of 47 000 and 44 000 cases per year, respectively,[33] these proportions suggest that about 4200 cases (9%) of bladder cancer per year and 6500 cases (18%) of rectal cancer per year are associated with the consumption of chlorinated water. The higher estimates for relative risk associated with more accurate assessment of exposure suggest that the true attributable proportions may be higher than those stated here.

Of the original papers included in the meta-analysis, only three of the seven bladder cancer studies and two of the six rectal cancer studies were statistically significant. Consequently, a standard review of the literature might conclude, erroneously, that no significant risk exists. Seemingly small risks posed by environmental factors may have major health impacts because of the large numbers of people exposed. The results of the meta-analysis demonstrate the utility of this methodology in the identification of important but elusive relative health risks and suggest that a wider application of meta-analysis is warranted.

Our findings are in no way intended to suggest that the disinfection of drinking water should be abandoned. The potential health risks of microbial contamination of drinking water greatly exceed the risks described above. Nonetheless, these findings should provide an impetus to identify, develop, and implement disinfection strategies that are not associated with adverse health effects. □

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Call for Abstracts for Injury Control/Emergency Services Late-Breaker Session

The Injury Control and Emergency Health Services Section will again sponsor a "late-breaker" session during the APHA 1992 annual meeting in Washington, DC. The session will be held on Tuesday, November 10, and will feature work completed within the last few months (after the deadline for consideration in the regular symposia of the APHA annual meeting).

Submit abstracts of 250 words or fewer (any format) and a return envelope to Richard Waxweiler, Division of Injury Control, Centers for Disease Control, Mail Stop F-36, Atlanta, GA 30333; tel. (404) 488-4690.

Abstracts must be received by September 1, 1992. Decisions will be made by September 15, 1992.